Foreword

Genetic Advances in Intellectual Disability

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Recently, the term *intellectual disability* (ID) has been suggested to replace *mental retardation*.[1]

ID is a generalized neurodevelopmental disorder originating before the age of 18 years, and characterized by significant limitations in intellectual and adaptive functioning, which covers many everyday social and practical skills; an IQ score below 70 in addition to deficits in two or more adaptive behaviors (conceptual, social, and practical skills) defines ID.

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), three criteria must be met for reaching a diagnosis of ID: deficits in general mental abilities, significant limitations in one or more areas of adaptive behavior across multiple environments (as measured by an adaptive behavior rating scale, i.e., communication, self-help skills, interpersonal skills, and more), and evidence that the limitations became apparent in childhood or adolescence. In general, people with ID have an IQ below 70, but clinical opinion may be necessary for individuals who have a somewhat higher IQ but obvious impairment in adaptive functioning.

Global developmental delay (GDD) is defined as a significant delay in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and it is thought to predict a future diagnosis of ID.[2]

The term *GDD* is used in children younger than 5 years, whereas in older children ID is usually applied.

Mild ID (IQ: 50–69) can be difficult to diagnose until the beginning of school[3]; as individuals reach adulthood, many can live independently. Moderate ID (IQ: 35–49) is evident within the first year of life. Speech delays are often the first sign, and these children need considerable supports in school, at home, and in the community.[3] People with severe or profound ID need more intensive support and they are easily recognized and diagnosed.

ID affects approximately 2 to 3% of the general population; in 75 to 90% of the cases, it is mild and in 30 to 50% it is nonsyndromic or idiopathic.[4]

ID can also be syndromic, associated with other medical and behavioral signs and symptoms. Williams syndrome and Rubinstein–Taybi syndrome are examples of syndromic ID.

In general, a genetic disorder is found in approximately 25% of cases.[4]

Causes of ID can include the following:

- *Infections (present at birth or occurring after birth)*: A pregnant woman who gets an infection such as rubella during pregnancy may have a baby with ID.
- *Genetic conditions*: The most prevalent include Down syndrome, Klinefelter syndrome, and Fragile X syndrome. There are a lot of different possible genetic conditions, some rare and some ultra-rare.
- *Metabolic (such as hyperbilirubinemia, very high bilirubin levels in babies)*: Metabolic disorder is another cause of ID in children.
- *Nutritional (such as malnutrition)*: Iodine deficiency is a preventable cause of ID.
- *Toxic*: A pregnant woman who drinks alcohol may have a child with the so-called fetal alcohol syndrome; also cocaine, amphetamines, and other drugs may give rise to a child with ID.
- *Problems at birth*: If a baby has a trauma or problems during labor and birth, such as not getting enough oxygen, an ID can develop caused by brain damage.
- *Unexplained problems*: There are also some unexplained causes of ID.

The classical approach to the patient must include the family history, with construction of a pedigree of three generations or more; the child's medical history (including prenatal and birth data); a dysmorphologic evaluation; and examination for neurologic or behavioral signs that might

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suggest a specific syndrome or diagnosis. After these, laboratory tests, imaging, and other consultations can be used for reaching the diagnosis and for care planning.

G-banded karyotyping historically has been the standard test for the search of genetic imbalance in patients with GDD/ID for more than 35 years. Currently, chromosomal microarray (CMA) is considered the first diagnostic test in all children with GDD/ID for whom the causal diagnosis is not known. Recently, Vissers et al reported the diagnostic rate of CMA to be at least twice that of the standard karyotype, and it is estimated at 12% for patients with GDD/ID.[5] It is important for the primary care pediatrician to collaborate with the clinical geneticist and the laboratory for the interpretation of CMA results, especially if "variants of unknown significance" are identified.[6,7]

Obviously, in the case of a specific clinical diagnostic suspect, the more detailed molecular analyses have to be done. For example, in boys with GDD/ID of uncertain cause, 2 to 3% will have fragile X syndrome (full mutation of FMR1, >200 CGG repeats), as will 1 to 2% of girls (full mutation).[8]

In few cases, also instrumental examinations can be helpful in reaching a diagnosis. For example, cerebral computed tomography or magnetic resonance imaging (MRI) can play a substantial role; currently, the literature does not indicate consensus on the role of neuroimaging, and recommendations include performing brain imaging on all patients with GDD/ID[9] or performing it only in those with indications on clinical evaluation.[10]

About 30% of children with ID have abnormal findings on MRI, but only in a fraction of these it leads to an etiologic or syndromic diagnosis.[11]

Although there is no specific medication for ID, there are various kinds of rehabilitation protocols[12]; moreover, many people, especially in syndromic disorders, have further medical complications to be monitored over time, and several medications may be prescribed.

For both pediatric primary care providers and families, there are recognized benefits establishing a specific diagnosis: clarification of etiology; definition of prognosis and natural history; definition of recurrence risks and treatment, also for possible complications; removal of unnecessary diagnostic tests; and provision of information about the presence of any specific support group.[13]

Until recently, the cause of ID remained unknown in at least 50% of affected people.

Our goal for this special issue in the *Journal of Pediatric Genetics* is to present readers with emerging new data on genetic advances in ID, which may help clinicians in the diagnosis and treatment of rare and ultra-rare syndromes. We begin with an update on next-generation sequencing (NGS) techniques in ID. Carvill et al in their article explain how NGS techniques have revolutionized gene discovery in patients with ID, leading to a large increase in knowledge of causal genes. They focus on syndromic and nonsyndromic ID and discuss the future of these intriguing new types of genetic research.

The next article in this issue by Edmondson et al reviews recent data regarding the overgrowth syndromes. This article describes the characteristic features of these overgrowth syndromes, as well as the current understanding of their molecular bases, intellectual outcomes, and cancer predispositions. Knowledge of the genetic bases of these syndromes provides useful insights into the normal regulation of growth and development.

The next two articles of the special issue specifically focus on neurocutaneous manifestations of genetic mosaicism and on the usefulness of hypertrichosis as a diagnostic clue.

Van Steensel discusses how skin manifestations can help in recognizing a neurocutaneous syndrome, with the obvious implications for diagnosis, counseling, and even treatment, with therapies targeted to specific pathways that are available for clinical use.

Pezzani et al make an overview of the main syndromes with hypertrichosis; this article aims to incentivize the clinicians to pay attention to the ectodermal annexes in patients with ID.

The subsequent reviews are on specific syndromes, and in particular Smith–Magenis and Potocki–Lupski syndromes, Pitt–Hopkins syndrome, and Rubinstein–Taybi syndrome.

The first review, by Neira and Potocki, is on two conditions which represent a model of antithetical genetic syndromes; the second, by Marangi and Zollino, deals with the intriguing and complex field of differential diagnosis of postnatal microcephalies; the third, by Spena et al, investigates the ultra-rare genetic syndromes, with the example of Rubinstein–Taybi syndrome.

In conclusion, knowing the cause enables genetic counseling and specific anticipation on healthcare needs. In recent years, the diagnostics advances in genetic conditions have provided great new opportunities in this way. The availability of array CGH has allowed the genome-wide detection of chromosomal aberrations. Until recently, the diagnosis of monogenic causes of ID was highly dependent on the recognizability of the phenotype; the introduction of exome sequencing allows testing of all genes (or a panel of genes) simultaneously in a single test. These developments may lead to a significant increase in the percentage of explained intellectual disability, from 50% in the past to 80%. However, contribution of clinician remains important in differential diagnosis and in the interpretation of genetic data, for genetic counseling and definition of natural history, with individualization of care for single syndromes and single patients.

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